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REMARKS

Claims 1-56 were pending prior to this response, with claims 1-42 and 41-56 being withdrawn due to a restriction requirement. By the present communication, claim 57 has been added, claims 35-36 and 38-39 have been cancelled, and claims 34, 37, and 40 have been amended to define Applicants' invention with greater particularity. The claim amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1-34, 37, and 40-57 are currently pending.

The Objection to the Claims

The Examiner has objected to the claims as containing subject matter that is drawn to a non-elected invention, the elected claims 34-40 allegedly being drawn to "a method of identifying an agent that modulates the expression or activity of BACE1 by comparing the phenotype of a transgenic A β 1-42 organism contacted with the agent to that of a BACE-1 knockout organism. Applicants submit that the division of the claims was excessively confusing (claims 34-40 having been divided into no less than nine different groups) and resulted in inadvertent election of group XVIII (claims 34-40) rather than group XIV (claims 34 and 37-40). By amendment herein claims 35 and 36 have been cancelled and additional claim amendments have been introduced to overcome certain rejections. As a result, the claims no longer fall into group XVIII subject matter and do fall into group XIV subject matter as set forth in the restriction requirement. Since the cancellation of claims 35 and 36 reduces the issue of whether a transgenic A β 1-42 organism can be produced, rather than introducing an issue that requires additional search, and further in view of the confusing nature of the division of the claims, Applicants respectfully request reconsideration and withdrawal of the objection to the claims in view of the restriction requirement.

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The Objection to the Declaration

The Office Action indicates that the Declaration is objected to by the Examiner (page 1). However, no basis for the objection is stated, so Applicants are at a loss to know how to correct any defect in the Declaration that might be the basis for the objection. Clarification is respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph – Description

Applicants respectfully traverse rejection of claims 34-40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 35-36 and 38-39 have been cancelled, rendering the rejection moot as to those claims. Therefore, Applicants will address the rejection as applied to claims 34, 37, 40 and 57.

Applicants disagree with the Examiner's assertion that the specification fails to contain sufficient description to provide those of skill in the art with the understanding that Applicant was in possession of the originally claimed invention because the specification describes only BACE1 knockout mice, and not other species of transgenic animals. In particular, Applicants disagree with the Examiner's assertion that the phenotype(s) of the claimed organisms cannot be predicted because the art of making knockout and transgenic organisms is highly unpredictable. Applicants respectfully submit that when function of a gene is disabled, production of the encoded protein ceases. Production of the encoded protein is a phenotype that can readily be measured by those of skill in the art, for instance, using an immunohistochemical approach.

However, to advance prosecution and reduce the issues, the pending claims have been amended to recite only a BACE1 knockout mouse as transgenic animal. The Examiner acknowledges Applicants' description of a BACE1 knockout mouse is adequate to meet the description test of 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection for alleged insufficient description of the subject matter of the claims.

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The Rejection under 35 U.S.C. § 112, First Paragraph – Enablement

Applicants respectfully traverse rejection of claims 34-40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 35-36 and 38-39 have been cancelled, rendering the rejection moot as to those claims. Therefore, Applicants will address the rejection as applied to claims 34, 37, 40 and 57.

Applicants disagree with the Examiner's assertion that the specification fails to contain sufficient description to enable those of skill in the art to make a BACE1 knockout organism for any species other than mouse because ES cells are required to practice gene targeting by homologous recombination as disclosed in the subject application, but ES cells are not available for species other than mice. This ground of the rejection is supported by Leonard et. al., 1995; Campbell and Wilmut, Jan. 1997; and Mullins et al., 1996, none of which cites a reference published later than 1996. Applicants point out, however, that the priority date of the subject application is October 2000, and that ES cells of various species were known as of the priority date of the subject application (see, for example, U.S. Pat. No. 6,103,523, rabbit ES cells; U.S. Pat. No. 6,271,436, porcine ES cells (see, also, U.S. Pat. No. 6,194,635); U.S. Pat. No. 6,200,806, primate ES cells; and U.S. Pat. No. 6,107,543, bovine ES cells). Thus, it is submitted that the skilled artisan, viewing the subject application as of the time it was filed, would have known that ES cells of various species could be obtained and that homologous recombination could be used in such ES cells to generate various species of transgenic (e.g. knockout) non-human animals. Accordingly, it is respectfully submitted that this ground of rejection should be removed.

However, to advance prosecution and reduce the issues, Applicants have amended the currently presented claims to limit the transgenic animals to a "BACE1-knockout mouse". The Examiner relies on M. Staufenbiel et al. as teaching that BACE1-knockout mice do not display the "phenotype" of cleaved A β peptides. However, the only result of the BACE1-knockout in the transgenic mouse as recited in the currently amended claims is a substantial decrease in expression or activity of BACE1 protein (See Specification, ¶ 0157) in mouse brain (See Example 7). The results of Applicants tests indicate that in wild-type mouse BACE1 protein

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expression is particularly localized to the brain, particularly to pre-synaptic terminals (§ [0188]); while BASE1 expression is substantially absent in the brain of a BASE1 knockout mouse. Thus, Applicants respectfully submit that a test agent that reduces the level of BASE1 expression or activity *in wild-type mouse brain* will be one that is a good candidate and merits further testing for utility in treatment of diseases associated with β -amyloid production in humans, such as Alzheimer's disease.

In view of the claim amendments and the above remarks, Applicants respectfully submit that that subject matter of amended claims 34, 37, and 40 and new claim 57 is fully enabled under 35 U.S.C. § 112, first paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 34-40 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite due to use of the term "substantially equal" in claim 34. Applicants submit that the U.S. Court of Appeals for the Federal Circuit recently upheld use of "substantially" in claim language (*Deering Precision Instruments L.L.C. v. Vector Distribution Systems Inc.*, CAFC, 10/17/03) (USPQ2d, Vol. 68, No. 7, 1716). In addition, there is a long history of acceptance of the term "substantially" in claim language. Therefore, Applicants submit that, as used in claim 34, the term "substantially equal" meets the definiteness test under 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims for alleged indefiniteness as applied to present claims 34, 37, 40 and 57.

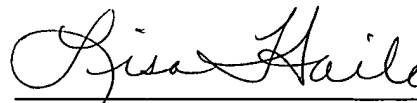
In summary, for the reasons set forth herein, Applicants maintain that claims 34, 37, 49 and 47 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

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If the Examiner would like to discuss any of the issues raised in the Office Action,
Applicant's representative can be reached at (858) 677-1456.

Respectfully submitted,

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